UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

REPLY TO DEFENDANTS' OPPOSITION TO PLAINTIFFS' *DAUBERT* MOTION TO PRECLUDE THE OPINIONS OF DEFENSE EXPERT STEVEN W. BAERTSCHI, PH.D.

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PRELIMINARY STATEMENT

Defendants attempt to explain away the methodological flaws of Dr. Baertschi by arguing that his opinion is "limited," because there is no other way to explain the gaps in his analysis. But even "limiting" his opinion does not cover the gaps. Defense asserts that the scope of Dr. Baertschi's opinions is narrow, and only includes: "Teva's conduct as a finished dose manufacturer" (Def. Opp. p. 7, 16); and "Teva's compliance with *pharmaceutical industry standards* in analyzing and testing its incoming valsartan API and *manufacturing finished dose valsartan products."* Def Opp., p. 9; see also Def. Opp. p 16. In a similar vein, the defense agrees that Dr. Baertschi is not opining on Teva's "regulatory compliance" or SOPs, nor on the conduct of ZHP, nor on cGMPs related to Teva's use of ZHP as an API supplier, whether Teva "could have" or "should have" detected the potential for the formation of nitrosamines through its risk assessment, or Teva's lack of testing of the ZHP API for genotoxins. Def. Opp., pp. 5, 11, 26; **Ex. B,** 203:6-11. Thus, Dr. Baertschi is left with a narrow field, and an incomplete and unreliable methodology.

Dr. Baertschi cannot opine that Teva acted as a "reasonably careful and prudent manufacturer in making, inspecting, and testing its valsartan products in connection with the process change implemented for ZHP API in 2014 and 2015" (**Ex. A**, ¶15) without a risk assessment of the chemical synthesis processes, compliance with cGMPs related to Teva's use of ZHP API, Teva's reliance on the

representations of ZHP, Teva's use and selection of ZHP as an API supplier, Teva's lack of testing the ZHP API for genotoxins, Teva's compliance with its own SOPs, or reviewing the actual chromatograms from Teva's testing of the ZHP API. Dr. Baertschi cannot opine Teva acted "reasonably and prudent in making, inspecting, and testing its finished valsartan products" when he admittedly has not considered all of the relevant evidence needed for such an opinion. **Ex. A**, ¶15. This is exactly what the *Daubert* standard is designed to prevent – opinions arrived at by ignoring evidence or standards that are inherent to or contrary to the expert's opinions. Defendants cannot limit Dr. Baertschi's opinions to only those standards by which he can say they complied.

[redacted] Consistent with no methodology, Dr. Baertschi never explained how source material was considered or weighted or why significant references and documents were chosen or left out of the report. Dr. Baertschi's redirect testimony that he used the same methodology in this case that he uses professionally does not fix his failure to objectively evaluate key relevant evidence and standards, or to speak in a relevant context framed by the applicable standards, required for a reliable methodology to satisfy *Daubert*.

Defendants' argument that "reading and analyzing" is the only methodology needed fails since Dr. Baertschi does not discuss why he chose to only use certain standards for his defense of Teva, while ignoring mandatory regulations, CFRs/cGMPs, and relevant FDA guidances such as Q9 Quality Risk Management (2006), Genotoxic and Carcinogenic Impurities in Drug Substances (2008), and Contract Manufacturing: Arrangements for Drugs/Quality Agreements (2013, 2016). Notably, even with the ICH guidances he cites, Dr. Baertschi is silent on the provisions within them that specifically state the thresholds upon which he relies do not apply to unusually toxic substances like NDMA and NDEA.[1] This highlights his biased selectivity, which warrants preclusion. See *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp.2d 398 (S.D.N.Y. 2005) at 425. His opinion is unhelpful and does not "fit" the case, as he supports it with Teva's compliance with *non-genotoxic* impurity levels as set forth by the USP and ICH guidances and ignores the fact that these permitted impurity levels do not apply to genotoxins like NDMA and NDEA. Such opinions are not based on "good grounds" and must be precluded. The defense misses the most relevant point in the Court's guidance on experts to wit: "So long as

[1] The USP specifically states that "any substance known to be toxic shall not be listed under the "Other Impurities" section of the Monograph and [redacted] **Ex. CC**; [redacted] The ICH Q3A and Q3B Guidelines dated 2006 provide for an exception to the impurity reporting threshold of 0.05%, identification threshold of 0.10% and qualification threshold of 0.15% for impurities that are unusually toxic like NDMA and NDEA. (See ICH Q3A(R2), p. 8 Attachment 1, Fn. 3 and ICH Q3B (R2) (p. 7, Notes on Attachment 1, Fn. 2) - **Ex. DD (Q3A)and Ex. MM (Q3B).**

they explain how they come to their opinions, **and so long as they attempt to explain why they didn't think contrary data is not relevant to their opinion,** then that's not objectionable."). 3/2/22 Ct. Hrg Tr., p. 148:8-17. Dr. Baertschi fails to meet this standard.

ARGUMENT

I. Dr. Baertschi's Failure to Consider or Analyze Evidence Important or Contrary to his Opinions Renders His Methodology Unreliable.

Courts routinely exclude expert testimony where the expert selectively chooses his support from the scientific landscape. *In re Rezulin Prods. Liab. Litig*., 369 F. Supp.2d 398 (S.D.N.Y. 2005) at 425. This is so because an expert who fails to consider important facts without satisfactory explanation warrants preclusion for unreliable methodology. *Player v. Motiva Enterprises, LLC*, 2006 WL 166452 at 6-7 (D.N.J. 2006). *Daubert* requires an expert account adequately for obvious alternative explanations because any theory that fails to explain information that casts doubt on that theory is inherently suspect. *In re Rezulin Prods. Liab. Litig*., 369 F. Supp.2d at 425. So if relevant scientific literature contains evidence tending to refute the expert's theory and the expert does not account for that evidence, the expert's opinion is unreliable. *Id*. *See also*, *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig*., 26 F. Supp.3d 449, 457 (E.D.Pa. 2014) (expert only "able to draw conclusions by ignoring the basic requirements of the relevant scientific community's methodology" held not to satisfy Rule 702).

Dr. Baertschi offers conclusory opinions that:

> Teva acted as a reasonably prudent and careful manufacturer in making, inspecting, and testing its finished valsartan products in connection with the process change implemented for ZHP API in 2014 and 2015.
>
> Teva acted as a reasonably prudent and careful manufacturer in inspecting and testing incoming valsartan API, including performing all testing required by the USP Monograph and ANDA, as well as all testing required and contemplated by genotoxic / mutagenic impurity guidances including ICH M7, and performing appropriate evaluation and testing of residual solvents. It was reasonable and appropriate for a finished dose manufacturer like Teva not to perform further analysis of unidentified peaks of the size seen on Teva's chromatograms of valsartan API batches that were ultimately determined to be NDMA/NDEA. **Ex. A,** ¶15 and 16.

In support of these very broad, conclusory opinions, Dr. Baertschi engages in a results-driven analysis by cherry-picking certain standards, guidance and evidence. This is illustrated by his failure to consider key evidence essential to forming these opinions such as: [redacted]

II. Dr. Baertschi has no reliable basis to opine that Teva performed appropriate evaluation and testing of its incoming valsartan API as he did not review Teva's residual solvent chromatograms.

Dr. Baertschi states: "It was reasonable and appropriate for a finished dose manufacturer like Teva not to perform further analysis of unidentified peaks of the size seen on Teva's chromatograms of valsartan API batches that were ultimately determined to be NDMA/NDEA." **Ex. A**, p. 28, ¶45. [redacted] The only way to evaluate unknown peaks - their frequency, location (retention time) and size – is to review the chromatograms.

Defendants address this omission by citing Dr. Baertschi's testimony claiming that ZHP used the same residual solvent method as Teva, so Teva would have gotten the same results, to justify Dr. Baertschi only reviewing ZHP's chromatograms for three valsartan API batches. Def. Opp. pp. 30-31; [redacted].

[redacted] Dr. Baertschi's pivot to this at his deposition is surprising because it disagrees with his report and evidence in this case. [redacted] makes Dr. Baertschi's assumption unreliable. There is simply "too great an analytical gap between the data and the opinion proffered," thus the opinion constitutes *ipse dixit* and should be excluded. See *GE v. Joiner*, 522 US 136 (1997) at 146.

To further illustrate the lack of an objective methodology, [redacted] were evaluated by the FDA and specifically referred to in the

[2] [redacted]

Warning Letter issued to ZHP. [redacted] Contrary to Dr. Baertschi's proffered opinions that the unknown peaks did not warrant further investigation, this is what the FDA says about these exact same chromatograms in reply to ZHP:

[redacted]

There is zero explanation provided by Dr. Baertschi as to the FDA statement that "if you investigated further, you may have found indicators in your residual solvent chromatograms alerting you to the presence of NDMA" or the FDA finding that there was at least one unidentified peak on each of these chromatograms that required further investigation. This again is an example of Dr. Baertschi's failure to address and explain information that otherwise would cast doubt on his theory, which makes his opinions inherently suspect. *In re Rezulin Prods. Liab. Litig.*, 369 F. Supp.2d 398 (S.D.N.Y. 2005) at 425; *Chen v. Yellen*, 2021 WL 4192078 (N.D. Ill. 2021) at 15 (Expert's selective reliance upon a set of facts while disregarding other relevant data is unreliable and subject to exclusion). As such, Dr. Baertschi's opinion that Teva acted as a reasonably prudent and careful manufacturer in making, inspecting, and testing its finished valsartan products must be precluded.

III. Dr. Baertschi's opinion that Teva's valsartan with NDMA/NDEA is the same as the RLD is not supported by a reliable methodology.

[redacted] The defense also argues that his opinion that Teva's valsartan was "the same as the RLD because the levels of all impurities were within the specification limits approved by the FDA via the ANDA." Def. Opp. p. 22. However, [redacted] USP Monograph have the same relevant impurity standards for identified, non-genotoxic impurities - total impurities (0.3%) and any other individual impurities (0.10%). See **Ex. AA** [redacted] His methodology fails because neither of the standards address NDMA or NDEA, nor the difference between the "approved' valsartan without NDMA and NDEA, and Teva's valsartan which undisputedly contained NDMA and NDEA. His reliance on compliance with the USP or ANDA impurity specifications is akin to Dr. Clevenger's unreliable methodology – the unreliable assertion that the absence of specifications setting forth limits for NDMA or NDEA in the USP Monograph and ANDA – must mean that the VCDs are the same as long as the drug product complies with the listed non-genotoxic impurity profiles. This is not a reasonable disagreement with Plaintiffs, it is a factually inaccurate position that is impermissible as a matter of law.

The USP does not allow for the presence of NDMA or NDEA under the impurity section, and the USP specifically states that "any substance known to be toxic shall not be listed under the "Other Impurities" section. **Ex. CC**. As such, one cannot rely on compliance with the USP impurity thresholds for unapproved, unidentified cohort-of-concern genotoxins.[3] [redacted] Using these impurity standards to justify "sameness," where they are not intended to and do not address the presence of unacceptable genotoxic impurities including NDMA or NDEA is fundamentally unreliable.

IV. Dr. Baertschi does not offer a reliable risk assessment opinion which is necessary to support his overall opinion.

The assertion plaintiffs do not challenge Dr. Baertschi's opinions regarding Teva's risk assessment is incorrect. An entire point of Plaintiff's Brief was devoted to precluding him from offering any risk assessment opinion. (Brief, p. 22, Point 4). Dr. Baertschi cannot opine Teva was a reasonably careful and prudent manufacturer

[3] USP has said, "their presence in medicines, even at trace level is considered unacceptable because Nitrosamine impurities are probable human carcinogens." USP, Summary, Highlights and Timeline of General Chapter <1469> Nitrosamine Impurities (July 20, 2018) – **Ex. RR.**

without substantively addressing risk assessment [redacted] Defendants concede that he does not opine on ZHP's risk assessment (Def. Opp. p. 24) or whether Teva "could have" or "should have" detected the potential for the formation of nitrosamines through its risk assessment. (Def. Opp. p. 26; **Ex. A** *Generally*). [redacted]

To reliably opine whether Teva acted as a "reasonably careful and prudent manufacturer in making, inspecting, and testing its valsartan products," Dr. Baertschi must address whether Teva with a proper risk assessment should have predicted nitrosamine formation. Contrary to defendants' assertions, [redacted]. It is the inadequacy of the failed risk assessments that is at issue.

To further illustrate the lack of a reliable methodology, Dr. Baertschi ignores important FDA findings of what a proper risk assessment of [redacted] One cannot reliably defend Teva's risk assessment without addressing these points.

Dr. Baertschi does not explain why Teva's risk assessment of ZHP's process change, which did not predict nitrosamine formation was reasonable, while ZHP's was deficient. Again, important contrary facts were not examined or explained. Dr. Baertschi's failure to substantively assess Teva's risk assessment and address contrary FDA findings renders his analysis and opinions as to Teva to be without good grounds or reliably based.

V. Dr. Hecht and Mr. Russ do not support Dr. Baertschi's opinion.

Defendants curiously refer to Dr. Hecht's testimony as somehow supporting their position. Dr. Hecht is an organic chemistry expert who is offering an opinion as to whether the risk assessment performed by ZHP constituted "a sound scientific appraisal of the chemical reactions involved in the synthesis, impurities associated with raw materials that could contribute to the impurity profile of the new drug substance, and possible degradation products" (**Ex. TT**, Hecht Tr. 294:10-296:8), not as a regulatory expert as to whether defendants' manufacturing practices or processes adhered to state and federal regulations or applicable regulatory guidances. Opp. Brief to Preclude Hecht, p. 11. To offer his opinions, Dr. Hecht did a thorough assessment of the chemistry involved in the synthesis processes and offers the opinion that nitrosamine formation was a predictable consequence of the reactions. Dr. Hecht testified that the chemists at ZHP "…didn't know what they were doing" and were "oblivious" when it came to assessing the risk of nitrosamine formation. **Ex. TT,** Hecht Tr. 76:1-11. This is hardly the endorsement of Defendants' conduct that they claim. Unlike Dr. Hecht, Dr. Baertschi has not employed a reliable methodology to offer opinions on a chemical risk assessment of the TEA or Zinc Chloride process. As set forth in detail in Plaintiffs' motion, it is not enough for [redacted]

[redacted]. These weak excuses have no reliable basis for examination or testing and are simply anecdotal and useless.

Moreover, Defendants' references to Dr. Hecht's testimony are misleading. Dr. Hecht's opinion is that a proper risk assessment would have identified potential nitrosamine formation and unknown peaks on residual solvent chromatograms should have been particularly suspect and led to further testing. Dr. Hecht does not state that the defendants were justified in ignoring the unknown peaks. The mischaracterization of Dr. Hecht's opinions should not distract from the real issues on this motion. Dr. Baertschi failed to review **Teva's chromatograms,** and as such he cannot offer any opinion as to what they did or did not show, and whether it was reasonable for Teva to ignore unknown peaks.

Defendants suggest plaintiffs' expert Philip Russ supports that Teva's valsartan was the same as the RLD because he "concedes" all levels of impurities for Teva valsartan were within the specification limits approved by the FDA via the ANDA. This is factually inaccurate. Mr. Russ merely agreed that he had seen no evidence that Teva's product did not comply with the listed *compendial specifications* but again the USP/compendial specifications do not include genotoxins, so this testimony does not speak to the issues on this motion. See **Defendants' Ex. B**, Russ Tr. 168:7-25; 169:9-14; 172:6-24.

VI. Dr. Baertschi's Deposition Errata sheets must be questioned.

In opposition to this motion, Defendants provided an Errata Sheet to Dr. Baertschi's 1/26/2023 deposition (**Def. Ex. C**) that was different from the Errata Sheet previously provided. [redacted]. This would be the appropriate standard to evaluate the adequacy of Teva's risk assessment which was not utilized by Dr. Baertschi.

CONCLUSION

For the foregoing reasons, Steven Baertschi, Ph.D. should be precluded from offering his opinions related to liability in this case.

Respectfully submitted on behalf of Plaintiffs,
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CERTIFICATE OF SERVICE

I hereby certify that on April 25, 2023, I electronically filed the foregoing document with the Clerk of the Court using the CM/ECF system which will send notifications of such filing to the CM/ECF participants registered to receive service in this MDL.

/s/ Rosemarie Riddell Bogdan

Rosemarie Riddell Bogdan